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# STUDIES ON CARDIOTOXIN AND VASOACTIVE SUBSTANCE RELEASING COMPONENT(S) OF COBRA VENOM

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# STUDIES ON CARDIOTOXIN AND VASOACTIVE SUBSTANCE RELASING COMPONENT(S) OF COBRA VENOM:

# COMPARISON OF HEMODYNAMIC EFFECTS OF CARDIOTOXIN WITH THOSE OF COBRA VENOM

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## ABSTRACT

The effects of cardiotoxin on the cardiovascular system has been studied in comparison with those of crude venom of Formosan cobra. The intravenous injection of cardiotoxin (1.0 mg/kg) usually produces an immediate rise in systemic arterial pressure, followed by a progressive decline leading to cardiac arrest, whereas a precipitous fall in systemic arterial pressure is usually observed with crude venom (0.5 - 1.0 mg/kg). A very marked increase in both pulmonary artery pressure and pulmonary vascular resistance is produced following the injection of crude venom, whereas the increase is far less conspicuous with cardiotoxin. Cardiac output as well as stroke volume is decreased by both crude venom and cardiotoxin. The early decrease in cardiac output with crude venom appears to be resulted from the marked increase in pulmonary vascular resistance, whereas the progressive decrease leading to circulatory failure is due to the direct effect of cardiotoxin on the heart. Ventricular contractile force is depressed by both crude venom and cardiotoxin, usually preceded by an initial augmentation of varying duration. Abnormal ECG changes such as ST depression, inverted T, nodal rhythm, A-V block, A-V dissociation, idioventricular rhythm and ventricular tachycardia are observed with cardiotoxin as well as crude venom. V. cava pressure is increased with crude venom probably as a result of dilatation of the right heart, whereas no appreciable change in caval pressure is found with cardiotoxin unless cardiac functions are seriously impaired at a later stage. Total peripheral resistance is increased and femoral artery flow decreased by cardiotoxin. An initial decrease in total peripheral resistance is often observed with crude venom. It is concluded that cardiotoxin is responsible for the initial pressor response as well as the cardiotoxic effects of cobra venom leading to cardiac arrest, whereas the early hypotensive effect of the venom appears to be due to some component(s) other than cardiotoxin.

Although the primary cause of death due to cobra venom has been shown to be peripheral paralysis in most animals (Kellaway et al, 1932; Lee and Peng, 1961; Vick et al., 1965), the venom also produces profound cardiovascular changes. Cats, being relatively resistant to cobra neurotoxin, die of cirulatory failure before the neurotoxin induces peripheral respiratory paralysis (Lee and Peng, 1961; Lee, 1963). Several active components such as neurotoxin, cardiotoxin, phospholipase A, and some proteins having other enzymatic activities have been separated from cobra venom (Lo et al, 1966; also see Meldrum, 1965; Boquet, 1966). However, it has not been established as to which component(s) or to what extent these components are responsible for the cardiovascular effects caused by cobra venom.

A cardiotoxic principle was first isolated from the Indian cobra venom by Sarkar (1947) and recently a more purified cardiotoxin has been obtained from the Formosan cobra venom by means of CM-Sephadex column chromatography (Lo et al. 1966), and its pharmacological properties have been studied in detail (Lee et al., 1968). In experiments reported herein, hemodynamic changes produced by cardiotoxin were analysed in comparison with those produced by the whole cobra venom, in order to elucidate the role played by cardiotoxin in the circulatory effects of cobra venom.

## MATERIALS AND METHODS

Venom The venom of Naja naja atra used in this study was freshly collected and lyophilized in this laboratory and stored in a vacuum desiccator.

Cardiotoxin Cardiotoxin was isolated from the crude venom by CM-Sephadex column chromatography according to the method of Lo et al. (1966), modified by Lee et al. (1968).

Experimental animals Cats of either sex, weighing from 1.5 to 3.4 Kg, were first lightly anesthetized with ether and then with 50 to 70 mg/kg of chloralose, injected into a cannulated femoral vein. The trachea was exposed and a tracheal cannula was inserted. When necessary, the animals were artificially respired with a Palmer pump. Cardiotoxin or the whole venom was injected into the left femoral vein.

Cardiac output, stroke volume, and total peripheral resistance A Statham M-4000 electromagnetic flowmeter was used to measure either aortic flow or pulmonary artery flow. The thorax was opened and the heart and great vessels were carefully exposed. A C-type flo-probe was placed around either the ascending aorta or the pulmonary artery close to the heart. Stroke volume was calculated by dividing either the aortic flow or pulmonary artery flow by heart rate. An estimate of total peripheral resistance was obtained by dividing mean

arterial pressure (mm Hg) by either aortic flow or pulmonary artery flow (ml/min).

Myocardial contractile force The force of ventricular contraction was measured with a Walton-Brodie strain gauge arch which was sutured to the surface of the left ventricle (Boniface et al., 1953). All sutures were so placed as to avoid occlusion of coronary vessels.

Pulmonary artery pressure and pulmonary vascular resistance A polyethylene cannula was inserted into the left pulmonary artery and the pressure was recorded by means of a Statham P23A transducer. The pulmonary vascular resistance was calculated by dividing mean pulmonary arterial pressure (mm Hg) by pulmonary artery flow (ml/min).

Vena cava pressure A polyethylene tubing was inserted into the left external jugular vein and advanced into the anterior cava, and the pressure was measured with the aid of a Statham P23B venous pressure transducer.

Femoral artery flow Femoral artery flow was measured using a Statham M-4000 electromagnetic flowmeter, the probe being placed around the right femoral artery just below the groin.

## RESULTS

### Systemic arterial blood pressure

Whole venom No remarkable changes in systemic arterial pressure were observed in five cats injected intravenously with 0.1 mg/kg of the whole venom. When the dose was increased to 0.5 mg/kg, a sharp fall in the mean arterial pressure began immediately following the injection and reached its lowest point (mean decrease of 38.7 per cent) between 30 sec to 2 min. The systolic pressure decreased more markedly than the diastolic one, so that the pulse pressure became smaller. Within 5 to 15 min, however, the blood pressure recovered toward the pre-injection levels and then decreased again gradually (Fig. 1). One out of five cats injected with this dose died of circulatory failure at 37 min after the injection. The mean decrease of carotid pressure during the second hypotensive phase was 20.8 per cent in the remaining four cats. The initial steep fall of blood pressure was absent when a second injection of the same dose was given after the effects of the first one had subsided, indicating the occurrence of tachyphylaxis to the initial hypotensive phase. The effects of the first injection with 1.0 mg/kg of the whole venom were qualitatively similar to those described above but quantitatively more pronounced and mostly irreversible. However, in five out of nine cats, in which 1.0 mg/kg was given after the effects of the previous injection with 0.5 mg/kg had subsided, a pressor effect was observed before the progressive

decrease of blood pressure ensued. The pressor effect was very marked in two cases (maximal increase of 60 to 98.8 per cent, lasting for 5 to 10 min) but only slight in three cases (less than 20 per cent increase, lasting for 2 to 10 min).

Cardiotoxin In contrast with the crude venom, 1.0 mg/kg of cardiotoxin almost invariably caused an initial rise followed by progressive fall in arterial pressure and finally cardiac arrest before respiratory failure (Fig. 2). The extent of the pressor effect varied from one animal to another and its duration was usually very transient, rarely exceeding 5 min. In three out of eleven cats, however, 1.0 mg/kg of cardiotoxin caused a precipitous fall in arterial pressure without an initial rise and death took place within a few min. The pressor effect as well as the progressive decrease in blood pressure could also be observed when 1.0 mg/kg of cardiotoxin was given after the effects of the previous injection with 0.5 mg/kg of either the whole venom or cardiotoxin had subsided, indicating no or little tachyphylaxis to both effects of cardiotoxin. With 0.5 mg/kg of cardiotoxin, both the initial rise and the following fall in arterial pressure were far less pronounced and no death was observed. With 0.1 mg/kg of cardiotoxin, no appreciable changes in arterial pressure were produced.

Vena cava pressure

Whole venom In three out of four cats, in which the systemic arterial pressure fell sharply on injection with 0.5 mg/kg of the whole venom, a very marked rise in the diastolic pressure of V. cava was found following the injection (Fig. 1). The rise in caval pressure took place almost simultaneously with the fall in carotid pressure except in one cat where the latter preceded the rise in caval pressure by 15 sec. As the carotid pressure recovered toward the pre-injection level within several minutes, the caval pressure also fell toward the control level. During the second hypotensive phase, however, the caval pressure remained almost unchanged. In the remaining cat which died 37 min after the injection no rise in caval pressure was observed until a few minutes before death. In four out of six cats injected with 1.0 mg/kg of the whole venom, the caval pressure rose markedly following the fall in carotid pressure and remained high without recovery until death. The rise in caval pressure appeared to be related to the impaired cardiac functions as revealed by ECG changes, such as A-V dissociation, atrial standstill, marked S-T depression, etc. In the remaining two cats, no marked changes in caval pressure were observed until a few minutes before death.

Cardiotoxin No appreciable changes in caval pressure were found with 0.5 mg/kg of cardiotoxin. Also in cats injected with 1.0 mg/kg of cardiotoxin, no rise in caval pressure was observed until their cardiac functions had been seriously impaired. In most animals the caval pressure rose markedly a few minutes before death.

Pulmonary artery pressure and pulmonary vascular resistance

Whole venom In all cats, pulmonary artery pressure as well as pulmonary vascular resistance markedly increased immediately on injection of the whole venom (0. 5 - 1. 0 mg/kg). The maximal increase of the mean pulmonary artery pressure varied between 36 to 290 per cent and that of pulmonary vascular resistance from 61 to 349 per cent. These changes took place closely either simultaneously with or prior to the initial maximal fall in carotid pressure (Fig. 3). The increase in pulmonary vascular resistance lasted longer than the rise in pulmonary artery pressure and persisted even after the latter fell a few minutes before death.

Cardiotoxin Although a rise in pulmonary artery pressure and an increase in pulmonary vascular resistance were also observed with cardiotoxin (0. 5 - 1. 0 mg/kg), these changes were far less conspicuous than those observed with the whole venom. The maximal increase of the mean pulmonary artery pressure varied from 20 to 95 per cent and that of pulmonary vascular resistance from 30. 6 to 81 per cent. In two cats in which 0. 5 mg/kg of the whole venom was given after the effects of the same dose of cardiotoxin had subsided, the average maximal increase in mean pulmonary artery pressure was 170 per cent with the whole venom as compared with 56 per cent with cardiotoxin. Moreover, there appeared to be no direct relation between the changes in systemic arterial pressure and those in pulmonary circulation caused by cardiotoxin, as the rise in pulmonary artery pressure took place during the initial rise in carotid pressure.

Cardiac output and stroke volume

Whole venom In all cats, cardiac output as well as stroke volume began to decrease within 30 sec following the injection of the whole venom (0. 5 - 1. 0 mg). The systemic arterial pressure and cardiac output followed similar patterns which appeared to be related chronologically to the increase in pulmonary circulatory resistance, especially during the early stage. With 0. 5 mg/kg, the inital sharp decline both in carotid pressure and cardiac output was usually followed by gradual recovery. With 1. 0 mg/kg, however, cardiac output decreased again progressively until death took place (Fig. 4).

Cardiotoxin With 0. 5 mg/kg of cardiotoxin, only a slight decrease not exceeding 30 per cent, was found in botn cardiac output and stroke volume. There was no such initial sharp decline as often seen with the crude venom. With 1. 0 mg/kg, despite of an initial rise in carotid pressure, also no increase in cardiac output was found. Both cardiac output and stroke volume decreased steadily until death (Fig. 5).

Contractile force

Whole venom Changes in contractile force varied from one cat to another. In two out of four cats injected with 1. 0 mg/kg of the whole venom, an initial increase in contractile force (15.7 and 30. 2 per cent respectively) was found 1 min

following the injection, and then progressive decrease followed. In the remaining two cats, only a decrease in contractile force was observed throughout the whole course. In three out of five cats injected with 0.5 mg/kg of the whole venom, an initial decrease (17.5 per cent in average) at 1 - 2 min after the injection was followed by an increase (17.2 per cent in average) from 5 to 10 min after the injection, and then it was followed by a decrease again. In one cat an increase in contractile force up to 20.6 per cent, lasting for about 15 min, was followed by a maximal decrease of 27.6 per cent. In the remaining cat, no increase in contractile force was observed.

Cardiotoxin In all four cats injected with 1.0 mg/kg of cardiotoxin, an initial augmentation in contractile force (an average of 34.9 per cent increase) of varying duration, from as short as 15 sec to as long as 20 min, was followed by progressive depression until death took place. In two out of four cats injected with 0.5 mg/kg of cardiotoxin, a slight increase (11.7 and 15.4 per cent respectively) was found 30 sec to 1 min after the injection and it was followed by a slight decrease (up to 11.8 and 14.3 per cent respectively) from 10 min after the injection. In one cat, however, the contractile force began to increase gradually up to 25 per cent from 10 min after the injection, following a very slight initial decrease of less than 5 per cent. In the remaining cat, only slight decrease, up to 10 per cent, was observed.

Heart rate and electrocardiogram

Whole venom In two out of five cats injected with 0.5 mg/kg of the whole venom, a transient increase in heart rate was observed immediately after the injection, which was followed by A-V dissociation within 1 min, while in the remaining three cats a decrease in heart rate with ST- and T changes was found 1 min after the injection. All of these changes almost recovered within 5 to 15 min after the injection. In one of the latter three cats, however, T wave became negative again and finally A-V dissociation appeared a few min before death. In the majority of cats injected with 1.0 mg/kg of the whole venom, a marked decrease in heart rate with ST- and T changes was found from 30 sec after the injection. In two cats with bilateral vagotomy, however, an increase instead of decrease in heart rate was observed. All cats injected with this dose died between 6 to 66 min after the injection. Various arrhythmias, such as S-A block, nodal rhythm, A-V block, A-V dissociation, idioventricular rhythm, ventricular tachycardia were observed before death.

Cardiotoxin With 0.5 mg/kg of cardiotoxin, no marked changes in ECG were found except a slight decrease in heart rate with moderate ST- and T changes. The heart rate usually returned to its pre-injection level within 5 to 15 min, while ST- and T changes persisted longer. The latter changes usually disappeared 20 to 50 min after the injection. With 1.0 mg/kg of cardiotoxin marked ST- and T changes were observed immediately following the injection. These changes became progressively severe and various arrhythmias described above appeared

sooner or later. However, no marked decrease in heart rate was usually observed until the later stage before death.

Total peripheral resistance

Whole venom Changes in total peripheral resistance were subject to considerable variation and were unpredictable with the whole venom. In three out of five cats injected with 0.5 mg/kg, a decrease in total peripheral resistance ranging from 18 to 24.5 per cent was observed concurrently with the inital sharp fall in carotid pressure. The total peripheral resistance either recovered or increased slightly as the carotid pressure returned toward the pre-injection level. In one cat, 30 sec following the injection, total peripheral resistance increased 84 per cent but this increase reduced to 19.8 per cent when the carotid pressure fell sharply 2 min after the injection. The total peripheral resistance increased again as the carotid pressure recovered toward the pre-injection level. All these findings indicate that during the initial fall in the systemic arterial pressure there was a decrease in total peripheral resistance. In two out of four cats injected with 1.0 mg/kg of the whole venom, total peripheral resistance at first decreased moderately (22.9 and 37.5 per cent respectively) for one or two min and then increased markedly (up to 260 and 331 per cent respectively) until death took place. In the remaining two cats, it increased moderately (37.6 and 45.5 per cent respectively) 30 sec following the injection and then began to decrease from 5 min after the injection. In one of them, however, it increased again from 15 min after the injection until death.

Cardiotoxin An increase in total peripheral resistance was invariably observed with cardiotoxin. With 0.5 mg/kg of cardiotoxin an average of 20.6 per cent increase in three cats was found from 1 to 10 min after the injection. With 1.0 mg/kg a marked increase in total peripheral resistance (up to 260 per cent) was observed during the initial rise in carotid pressure.

Femoral artery flow

Whole venom With 0.5 mg/kg of the whole venom, femoral artery flow fell rapidly by an average of 38.3 per cent in five cats. Although a decrease in total peripheral resistance was observed during the initial fall in the systemic arterial pressure, no increase in femoral artery flow was found. With 1.0 mg/kg, the flow decreased progressively to unmeasurable level before death.

Cardiotoxin With 0.5 mg/kg of cardiotoxin, femoral artery flow decreased gradually by an average of 47 per cent in three cats. With 1.0 mg/kg of cardiotoxin, the flow fell sharply during the initial rise in carotid pressure and continued to decrease until death.

## DISCUSSION

Different effects have been observed on the arterial blood pressure with cobra venom. The most conspicuous and consistent cardiovascular change produced by cobra venom is an immediate and profound fall in systemic arterial pressure (Chopra and Iswariah, 1931; Iwase, 1933; Gautrelet and Halpern, 1934; Gautrelet, Halpern and Cortiggiani, 1934; Feldberg and Kellaway, 1937a, 1937b, 1938; Peng, 1955a; Westermann and Klapper, 1960; Lee and Peng, 1961). The animals may die of circulatory failure in a few minutes if the dose is large enough (Chopra and Iswariah, 1931; Feldberg and Kellaway, 1937a, 1937b, 1938), but partial recovery usually takes place. Most animals except the cat eventually die of peripheral respiratory paralysis (Lee and Peng, 1961) and a rise in arterial pressure due to asphyxia is observed before death (Iwase, 1933; Peng, 1952). Apart from the rise in blood pressure before death, a pressor effect has also been obtained in cats and rabbits during the early stage with Indian cobra venom (Elliot, 1904; Epstein, 1930; Chopra and Iswariah, 1931; Venkatacholom and Ratnagiriswaran, 1934; Gottdenker and Wachstein, 1940; Sarkar, Mitra and Ghosh, 1942). However, no such pressor effect has been reported with Formosan cobra venom (Iwase, 1933; Peng, 1952).

In the present study both pressor and depressor effects were observed in cats with cardiotoxin whereas a pressor response was rarely observed with the whole venom unless a second dose was given after the depressor effect of the previous injection had subsided. The pressor response is apparently due to vasoconstriction caused by cardiotoxin (Lee et al., 1968), since total peripheral resistance is increased and cardiac output is decreased by cardiotoxin. Besides cardiotoxin, the crude cobra venom contains various constituents, such as nucleosides, phospholipase A and other enzymes (Lo, Chen and Lee, 1966), which may be responsible for the early depressor effect of the venom. The presence of constituents with opposite effects in the venom can also be appreciated from the findings that total peripheral resistance changes in both directions with the whole venom. When tachyphylaxis to the initial hypotensive effect occurs, the pressor response may be uncovered following the second injection with the whole venom. The initial hypotensive effect of cobra venom appears to be chiefly due to a decrease in cardiac output and partly due to a decrease in total peripheral resistance. The decrease in cardiac output at this stage is apparently due to reduced blood return from the pulmonary circuit, resulted from a marked increase in pulmonary vascular resistance. The latter appears to be also responsible for the increase in caval pressure by causing dilatation of the right heart. It remains to be elucidated, however, whether these effects are caused by the venom itself, or mediated by histamine liberation from the tissues as suggested by Feldberg and Kellaway (1938). Since no decrease in heart rate was observed in the vagotomized cats, at least some of these effects appears to be due to vagal reflex, as claimed by Westermann and Klapper (1961). Although a rise in pulmonary artery pressure was also observed with cardiotoxin, it was far less prominent and no

appreciable changes in caval pressure were found with cardiotoxin unless cardiac functions were seriously impaired at a later stage. Moreover, there appears to be no correlation between the changes in pulmonary circulation and those in systemic arterial pressure caused by cardiotoxin.

On the other hand, the progressive fall of systemic arterial pressure leading to circulatory failure and death appears to be chiefly, if not entirely, due to the 3 cardiotoxic components contained in the venom (Lee et al., 1968). In fact, all of the abnormal ECG findings observed with the whole venom, such as ST- and T changes, nodal rhythm, A-V block, A-V dissociation, idioventricular rhythm and ventricular tachycardia, could be reproduced with cardiotoxin. In addition, both the crude venom and cardiotoxin caused progressive decrease in cardiac output and stroke volume until death took place.

It is concluded from the results of the present investigation that cardiotoxin is responsible for the initial pressor response as well as the cardiotoxic effects of cobra venom leading to circulartory failure and death in cats, whereas the early hypotensive effect of the venom appears to be due to some component(s) other than cardiotoxin.

## SUMMARY

1. The effects of cardiotoxin on the cardiovascular system has been studied in comparison with those of crude venom of Formosan cobra.

2. The intravenous injection of cardiotoxin (1.0 mg/kg) usually produces an immediate rise in systemic arterial pressure, followed by a progressive decline leading to cardiac arrest, whereas a precipitous fall in systemic arterial pressure is usually observed initially with crude venom (0.5 - 1.0 mg/kg)

3. The pressor effect can also be found with crude venom (1.0 mg/kg) if tachyphylaxis to the early depressor effect occurs after the previous injection of a smaller dose.

4. A very marked increase in both pulmonary artery pressure and pulmonary vascular resistance is produced following the injection of crude venom, whereas the increase is far less conspicuous with cardiotoxin.

5. Cardiac output as well as stroke volume is decreased by both crude venom and cardiotoxin. The early decrease in cardiac output with crude venom appears to be resulted from the marked increase in pulmonary vascular resistance, whereas the progressive decrease leading to circulatory failure is due to the direct effect of cardiotoxin on the heart.

6. Ventricular contractile force is depressed by both crude venom and cardiotoxin, usually preceded by an initial augmentation of varying duration.

7. The heart rate is decreased and abnormal ECG changes, such as ST depression, inverted T, nodal rhythm, A-V block, A-V dissociation, idioventricular rhythm and ventricular tachycardia, are observed with cardiotoxin as well as crude venom.

8. V. cava pressure is increased with crude venom probably as a result of dilation of the right heart, whereas no appreciable change in caval pressure is found with cardiotoxin unless cardiac functions are seriously impaired at a later stage.

9. Total peripheral resistance is increased and femoral artery flow decreased by cardiotoxin. An initial decrease in total peripheral resistance is often observed with crude venom.

10. It is concluded that cardiotoxin is responsible for the initial pressor response as well as the cardiotoxic effects of cobra venom leading to cardiac arrest, whereas the early hypotensive effect of the venom appears to be due to some component(s) other than cardiotoxin.

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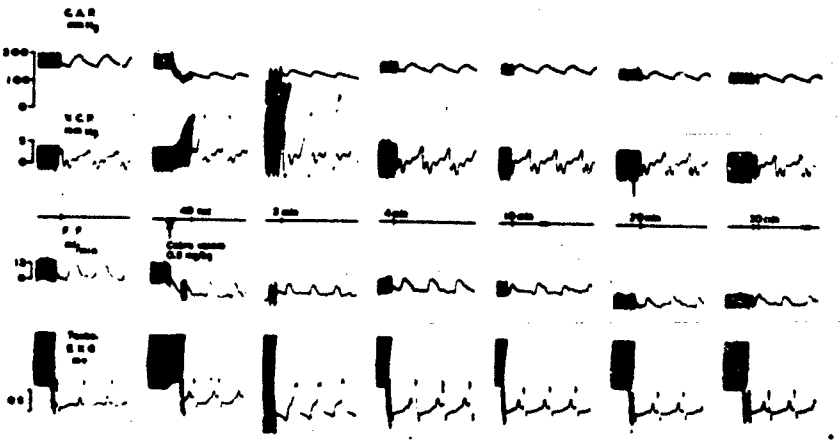

Fig. 1. Representative records showing effects of cobra venom (0.5 mg/kg) on carotid arterial pressure (C. A. P.), V. cava pressure (V. C. P.), femoral artery flow (F. F.), and electrocardio grams (E. K. G.). Cat No. 11, 1.8 kg; chloralose 50 mg/kg i. v. Injection of the venom is marked by the arrow. In this and subsequent tracings, slow speed; 0.25 mm/sec and fast speed; 50 mm/sec.

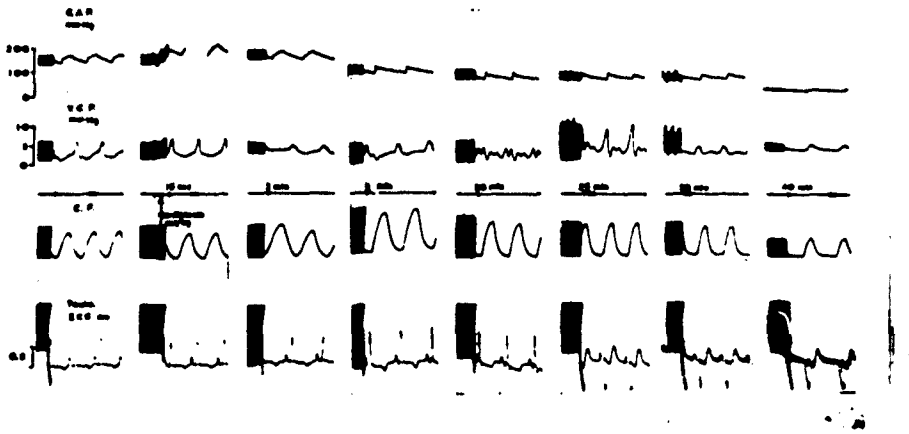

Fig. 2. Representative records showing effects of cardiotoxin (1 mg/kg) on carotid arterial pressure (C. A. P.), V. cava pressure (V. C. P.), ventricular contractile force (C. F.), and electrocardiograms (E, K. G.). Cat No. 30, 2. 0 kg; chloralose 50 mg/kg i. v. Injection of cardiotoxin is marked by the arrow.

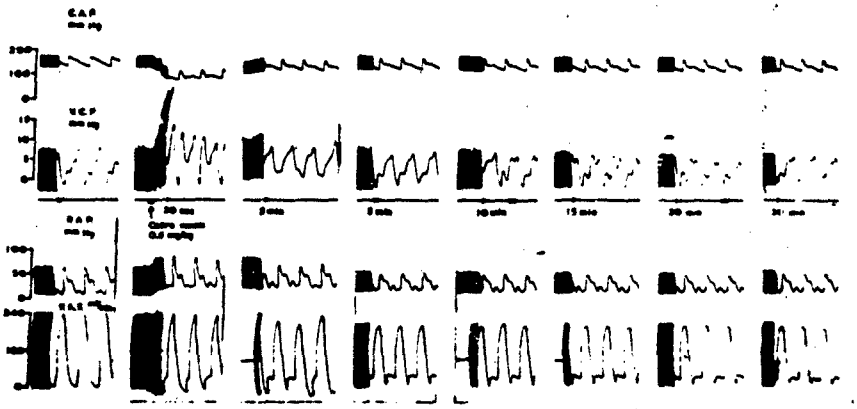

Fig. 3. Effects of cobra venom (0.5 mg/kg) on carotid arterial pressure (C. A. P.), V. cava pressure (V. C.), pulmonary artery pressure (P. A. P.) and flow (P. A. F.). Cat No. 18, 2.3 kg; chloroalose 50 mg/kg, i. v. Injection of the venom is marked by the arrow.

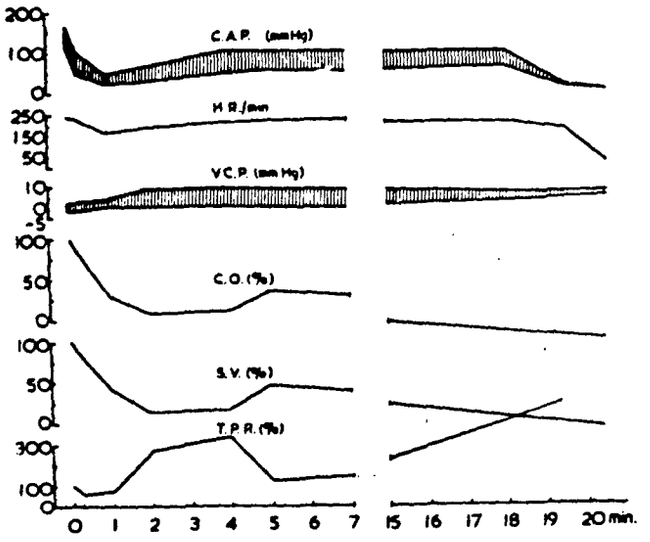


Fig. 4. Effects of cobra venom (1.0 mg/kg) on carotid arterial pressure (C. A. P.), heart rate (H. R.), V. cava pressure (V. C. P.), cardiac output (C. O.), stroke volume (S. V.), and total peripheral resistance (T. P. R.). Cat No. 26, 1.91 kg; chloralose 50 mg/kg, i. v. The venom was injected at O time.

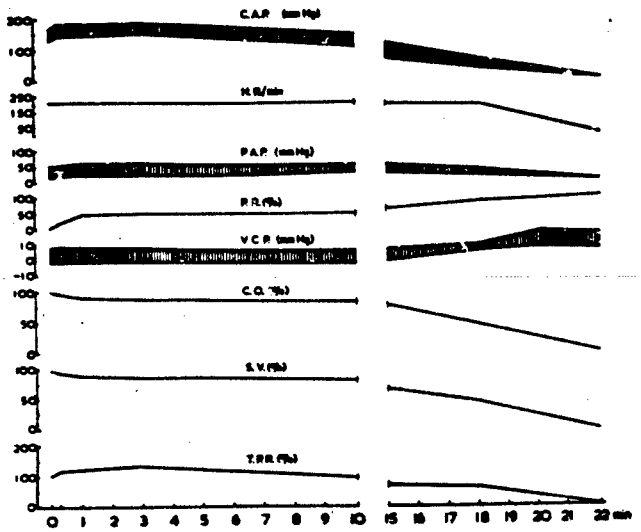


Fig. 5. Effects of cardiotoxin (1.0 mg/kg) on carotid arterial pressure (C. A. P.), heart rate (H. R.), pulmonary artery pressure (P. A. P.), pulmonary resistance (P. R.), V. cava pressure (V. C. P.), pulmonary artery flow (C. O.), stroke volume (S. V.) and total peripheral resistance (T. P. R.). Cat No. 19, 2.0 kg; chloralose 50 mg/kg, i. v. Cardiotoxin was injected at O time.